REMARKS

The undersigned takes this opportunity to thank Examiners Yaen and Nickol for the courtesies extended in the interview on 3/25/2004. It is believed the discussion was beneficial for advancing prosecution of the present application. The outstanding 112, enablement rejection and 103 rejection were both discussed at the interview.

35 USC Section 112, first paragraph

Claims 26, 28-34 and 37-51 are rejected under 35 USC Section 112, first paragraph on the basis that the specification, while being enabling for a method of treating cancer comprising the administration of rhuMAb HER2 (Herceptin®), does not reasonably provide enablement for a method of treating cancer with any HER2 antibody.

Applicants submit that the invention set forth in claims 26, 28-34 and 37-51 was enabled by the present specification at the time of filing.

The Examiner urges the specification is not enabling for any and all forms of anti-HER2 antibodies.

Applicants explained at the interview that the specification should be evaluated in view of the state in the art **at the filing date, namely 1995.** By that time, the state of the art with respect to HER2 antibodies was well established. For example, Shepard *et al. J. Clin. Immunol.* 11(3):117-127 (1991), relied on by the Office in the 103 rejection, described several antibodies other than 4D5/Herceptin® (*e.g.*, 3E8, 7F3 and 3H4; Tables II and III), that inhibited proliferation of HER2 overexpressing tumor cells, which could have been used in the presently claimed methods. See, also, US Patent 5,725,856 (Hudziak *et al.*, of record) a patent application filed in 1988 and discussed at the interview, which, aside from describing 4D5, also refers to antibodies 3E8 and 3H4 that inhibit growth of cancer cells expressing HER2 (Fig. 3 of Hudziak *et al.*) and reports that 3E8 "gives 100% tumor growth inhibition" in an *in vivo* tumor model

(Hudziak *et al.* at column 19, line 37). The specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. See MPEP 2164.05(a), and the cases cited therein. Hence, Applicants submit that the disclosure of the present application coupled with the state of the art in 1995 would have enabled the presently claimed methods using antibodies other than 4D5/Herceptin®.

As to Shepard *et al.*, the Examiner urges that "not all HER2 antibodies are effective in the inhibition of tumor cell proliferation/growth," that 6E9 "had little effect in the inhibition of tumor cell over control antibodies," and that "2 of 6 antibodies showed little difference in inhibiting cellular proliferation when compared to cell lines lacking the HER2 receptor indicating that not all HER2 antibodies are functionally equivalent."

Applicants agree that not all HER2 antibodies are functionally equivalent, but the present application, coupled with what was known in the art in 1995, including Shepard *et al.*, published in 1991, would have enabled the skilled person to screen for antibodies, including 4D5/Herceptin® and others, that could be formulated and used in the presently claimed methods. Indeed, 4 of the 6 antibodies in Shepard *et al.* were able to inhibit tumor growth. Hence, Applicants submit that Shepard *et al.* supports the enablement of the presently claimed methods.

With respect to Stancovski *et al. PNAS USA* 88: 8691-8695 (1991), and its disclosure of a stimulatory HER2 antibody, the Examiner contends "the claims do not recite any specific limitation that would necessarily exclude from the HER2 antibodies the stimulatory antibody taught by Stancovski *et al.*" The undersigned explained at the interview, and Examiner Nickol agreed, that since the claims concern a "method for *treating*" a cancer or ductal carcinoma *in situ*, comprising administering a "*therapeutically effective* amount," the claims do

exclude therapeutically ineffective antibodies.

Hence, Applicants submit that the presently claimed invention would have been enabled by the present application at the filing date. Reconsideration and withdrawal of the Section 112, first paragraph rejection is respectfully requested.

35 USC Section 103

Claims 26, 28, 37-43 and 51 are rejected under 35 USC Section 103(a) as being unpatentable over Shepard *et al. J. Clin. Immunol.* 11(3):117-127 (1991); in view of Draber *et al. J. Immunol. Methods* 181(1): 37-43 (1995); Sato *et al. Cancer* 70(10): 2493-8 (1992); Nielsen *et al. Am. J. Clin. Pathol.* 102(1):76-9 (1994); Natali *et al. Int. J. Cancer* 45:457-461 (1990); and Roy *et al. Dev. Biol. Stand.* 74:323-329 (1992).

Applicants submit that the invention set forth in claims 26, 28, 37-43 and 51 is patentable over the cited art.

Independent claims 37 and 42 concern therapy of certain cancers (claim 37) or ductal carcinoma *in situ* (claim 42) comprising administering a HER2 antibody formulation, wherein the molar ratio of lyoprotectant:antibody is 100-600 mole lyoprotectant:1 mole antibody.

The undersigned explained at the interview that selection of the presently claimed, low, molar ratio of lyoprotectant:antibody was not obvious from the cited references at the time of filing.

The primary reference upon which the Examiner relies for the proposition that the molar ratio would have been obvious is Draber *et al.* However, not only is the molar ratio in Draber *et al.* much higher - *i.e.* much more sugar:antibody is used - but Draber *et al.* also **teaches away** from reducing the amount of sugar used.

Draber *et al.* refers to freeze-drying IgM supernatants (5-50µg/ml IgM antibody) or ascitic fluid (1-15 mg/ml IgM) (see page 40 of this reference). Page 39 of Draber *et al.* states that the concentration of trehalose was routinely 0.25M. Assuming a 950,000 molecular mass for the IgM pentamer, the molar ratios of trehalose to IgM are as follows.

Trehalose:IgM in Draber *et al.*	**Molar ratio**
0.25M trehalose: 5 µg/ml IgM	$4.7 \times 10^7 : 1^a$
0.25M trehalose: 50 µg/ml IgM	$4.7 \times 10^6 : 1^b$
0.25M trehalose: 1/mg/ml IgM	$2.4 \times 10^5 : 1^c$
0.25M trehalose: 15/mg/ml IgM	$1.6 \times 10^4 : 1^d$

(a) 5 µg/mL = 0.005 g/L which after dividing by 950,000 g/mole = 0.53×10^{-8} M. Thus 0.25 M trehalose/0.53×10^{-8} M IgM= 4.7×10^7. (b) Then for 50 µg/mL, the ratio is 4.7×10^6. (c) IgM at 1 mg/mL = 1 g/L which after dividing by 950,000 g/mole = 1.05×10^{-6} M. Thus, 0.25 M trehalose/1.05×10^{-6} M IgM = 2.4×10^5. (d) Then for 15 mg/mL the ratio is $2.4 \times 10^5/15 = 1.6 \times 10^4$.

Clearly, the molar ratios of trehalose:IgM in Draber *et al.* significantly exceed the lyoprotectant:antibody, 100-600:1 molar ratio in claims 37 and 42.

At the interview, the Examiner indicated his calculations may differ from those set forth above. Applicants believe the above calculations are accurate, but if the Examiner can point out where his calculations differ, Applicants will be happy to address this.

While the Examiner suggests that "one of skill in the art would have been motivated to play with the ranges so as to minimize the amount of lyoprotectant added to an antibody formulation," Applicants submit that the art at the time of filing **cautioned against** playing with the ranges. Specifically, Draber warns against not including 0.25M trehalose, because otherwise the antibodies will "quickly [lose]

binding activity on 4°C storage or become partially denatured during freezing and thawing" (Draber *et al.*, first paragraph of "Results" on page 39).

Reconsideration and withdrawal of the Section 103 rejection of claims 37 and 42, and the claims which depend thereon, is respectfully requested in view of the above.

Applicants turn now to **claim 51**. This claim represents a combination of claim 37 and claim 45, and claim 45 is not rejected under 103, so Applicants believe that claim 51 is likewise acknowledged to be patentable over the cited art. Examiner Yaen said he would look into this.

Applicants submit that the rejection of claim 51 should be withdrawn in that the Office has not shown how the prior art taught a formulation comprising a HER2 antibody in an amount from about 5-40mg/mL, sucrose or trehalose in an amount from about 10-100mM, a buffer and a surfactant. See also claim 26 of related US Patent No. 6,267,958.

Applicants respectfully submit that claims 26, 28, 37-43 and 51 are patentable over the cited art, and reconsideration and withdrawal of the Section 103 rejection is requested.

Serial No.: 09/648,896

Applicants look forward to receipt of the notice of allowance in due course.

Respectfully submitted,
GENENTECH, INC.

Date: April 2, 2004

By: Wm Lee

Wendy M. Lee
Reg. No. 40,378
Telephone: (650) 225-1994

09157
PATENT TRADEMARK OFFICE